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Rationale and design of DUAL study: Doxycycline to Upgrade response in light chain (AL) amyloidosis (DUAL): A phase 2 pilot study of a two-pronged approach of prolonged doxycycline with plasma cell-directed therapy in the treatment of AL amyloidosis

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ABSTRACT

Light chain (AL) amyloidosis is a plasma cell neoplasm associated with insoluble fibril deposition from clonal immunoglobulin chains systemically. The disease is associated with high early mortality and morbidity owing to advanced organ deposition as well as lack of proven de-fibrillogenic therapies. Pre-clinical and retrospective clinical data suggests that doxycycline has benefit in AL amyloidosis. The ongoing DUAL study is a single center, open label, phase 2 study in which patients with AL amyloidosis who are undergoing clone-directed therapy for the underlying neoplasm with oral doxycycline given for 1 year to test the hypothesis that prolonged doxycycline use will be safe, feasible, and lead to reduced early mortality in systemic AL amyloidosis and hasten organ amyloid response. Clinical follow up visits will occur at monthly intervals for systemic AL patients and at 3 monthly intervals for localized AL patients. Blood tests will be collected during these time points for hematologic response assessment. Organ testing will be conducted at 3 monthly intervals and radiologic testing will be conducted at 6 monthly intervals. Research blood samples will be collected at baseline, 6 and 12 months. Other correlative studies include matrix metalloproteinases (MMP), tissue inhibitor of metalloproteinases (TIMP) testing and patient-reported outcomes.

1. Introduction

The amyloidoses are a diverse group of protein misfolding diseases wherein proteins aggregate and form insoluble, fibrillar deposits (amyloid) in tissues [1]. Examples of amyloid diseases include Alzheimer's disease, hereditary transthyretrin-associated familial amyloid polyneuropathy, dialysis related amyloidosis, AA amyloidosis with chronic systemic inflammatory states and immunoglobulin-derived light chain (AL) amyloidosis. Human amyloid-associated illnesses pose a therapeutic challenge since amyloid is a long-lived protein and there are no approved drugs demonstrated to disrupt pre-formed amyloid.

Light chain amyloidosis is a malignant plasma cell disease characterized by the formation of amyloid from immunoglobulin light chains produced by clonal plasma cells [1]. The amyloid deposits into vital organs such as the heart, liver, kidney, and nerves resulting in multisystemic decline in function and culminating in death. Of the 31 currently known extracellular proteins resulting in amyloidosis in humans, AL amyloidosis is the most common in the developed world and the most rapidly fatal with a median survival of 6 months in advanced disease [1,2]. Current therapies used in AL amyloidosis eradicate cells that produce AL amyloid protein but have no effect on pre-formed amyloid. This produces a hematologic response by clearing circulating immunoglobulin light chains which would have eventually been deposited into amyloid. Treatments range from high dose therapy with autologous stem cell transplantation in eligible patients [3], or anti-myeloma chemotherapies. Novel anti-myeloma agents have excellent anti-plasma cell efficacy in amyloidosis but are also associated with organ and tissue toxicity making their use in clinical practice challenging, particularly in advanced AL disease [4]. One of the critical unmet needs of AL amyloidosis therapy is early mortality in patients,

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Table 1
Systemic AL amyloidosis.

	Baseline[a]	Months												End of Treatment (within 30 days)
		1[a]	2	3	4	5	6	7	8	9	10	11	12	
Inclusion & Exclusion criteria	×													
Informed consent	×													
H & PE[d]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Vital signs[e] eee	×	×	×	×	×	×	×	×	×	×	×	×	×	×
ECOG performance status	×			×			×			×			×	×
NYHA class	×						×[k]						×[k]	×[k]
Complete Blood Count with differential	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Serum chemistries panel[f]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Amyloid subtype[b]	×													
β_2 microglobulin	×													
Myeloma screening panel[g]	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Bone marrow aspirate/biopsy	×[j]													
B-HCG serum pregnancy test[h]	×													
Bone survey[n]	×[j]													
2D echocardiogram (IVS + LVEF)	×						×[k]							×[k,c]
Troponin-T, NT-proBNP	×	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k]	×[k,c]
Abdominal Imaging	×[j]						×[l]							×[l,c]
24 h urinary protein with UPEP/immunofixation	×			×[m]			×[m]			×[m]				×[m,c]
Toxicity assessment		×	×	×	×	×	×	×	×	×	×	×	×	
Research specimens[i]	×							×						×[c]
Patient-reported outcomes[o]	×	×	×	×	×	×	×	×	×	×	×	×	×	×

H & PE = history and physical examination.
ECOG- Eastern Co-operative Oncology Group performance score.
NYHA- New York Heart Association Class.
2D echocardiogram- Two-dimensional transthoracic echocardiogram.
IVS- interventricular septal thickness.
LVEF- left ventricular ejection fraction.

[a] Baseline and Month 1 can occur within 7 days without the need to repeat the Month 1 testing.
[b] If a patient has had amyloid subtyping performed in the past, this need not be repeated again.
[c] May be performed anytime during cycle 12 or within 30 days of the last dose of doxycycline.
[d] History is only required at baseline.
[e] Vital signs: blood pressure, pulse rate, respiratory rate and temperature.
[f] Serum chemistries panel: electrolytes, BUN, ALT, AST, creatinine, bilirubin, alkaline phosphatase, LDH, albumin, uric acid. Electrolytes to include sodium, potassium, chloride, carbon dioxide, and calcium.
[g] Myeloma screening panel includes serum protein electrophoresis, immunofixation electrophoresis, free light chain assay.
[h] Females of reproductive potential only.
[i] Peripheral blood specimens: 6 mL blood in heparin containing tube at indicated time points and send to the Tissue Bank at MCW after processing.
[j] May be performed within 3 months of baseline.
[k] Cardiac assessment will be followed only if baseline cardiac involvement.
[l] Abdominal imaging will be repeated only if baseline liver involvement.
[m] Urinary studies will be repeated only if baseline renal involvement.
[n] Not required if ≤ 10% plasma cells in bone marrow.
[o] PROMIS Global Health Scale, PROMIS-29, PROMIS Fatigue-8 short forms.

particularly those with advanced stage amyloidosis; this has remained unchanged since the 1970s [5] despite the availability of more effective anti-myeloma chemotherapy that have clearly improved myeloma outcomes during the same time frame [6]. Thus, consideration of therapies that complement current cytotoxic anti-amyloid treatment by hastening organ response is required.

Doxycyline is a semisynthetic tetracycline developed for antibacterial use; an effect primarily mediated by binding to the bacterial ribosome and inhibiting protein synthesis. Separate from their antimicrobial effect, tetracyclines also possess the ability to inhibit members of the matrix metalloproteinase (MMP) family of endopeptidases. The MMPs are zinc-dependent proteases involved in a gamut of physiological and pathophysiological processes such as embryogenesis, tissue remodeling, inflammation and tumor invasion [7]. It is hypothesized that overproduction of MMPs can result in AL renal and cardiac damage [8,9]. High levels of MMPs appear to correlate with diastolic dysfunction and clinical manifestations of AL cardiomyopathy [9]. Doxycycline-induced inhibition of MMPs appears to be beneficial in conditions associated with pathologic MMP-mediated proteolysis of the extracellular matrix, including cardiac remodeling, periodontitis, arthritis and cancer [10–12]. Owing to its lipophilicity, doxycycline also concentrates in organs at sites of injury including gums in gingivitis, brain in meningitis and the myocardium in infarcts [13]. The first report of the anti-amyloidogenic activity of doxycycline was suggested in a study of Alzheimer's disease [14]. Forloni et al., showed that co-incubation of tetracyclines with β 1–42 synthetic peptide, which is highly represented in Alzheimer amyloid deposits, resulted in a) marked reduction of amyloid fibril formation, b) inhibition of amyloid aggregation and c) de-fibrillogenic effect against pre-formed amyloid fibrils [14]. Cardoso et al. tested various tetracyclines and showed doxycycline to be the most effective of the family in disrupting transthyretrin amyloid fibrils after incubation [15]. This group also showed that the anti-amyloid effect is independent of the amyloid precursor protein [16]. Doxycycline also disrupted amyloid in animal models, including a familial amyloid polyneuropathy transgenic mouse model [17]. Further studies showed that tetracyclines also produced destructuration of β2-microglobulin in dialysis related amyloidosis [18]. In AL amyloidosis, Ward, et al. showed that doxycycline can inhibit amyloid fibril aggregation and can destroy preformed amyloid in vitro and in a transgenic murine AL model [19].

Doxycycline is well-tolerated and safe, and is widely used in clinical practice for antibacterial prophylaxis, community acquired pneumonia and chronic obstructive pulmonary disease. It is also efficacious in unusual infections such as Lyme disease, cholera, syphilis, plague and